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Platelet transactivation by monocytes promotes thrombosis in heparin-induced thrombocytopenia

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Abstract

© 2016 by The American Society of Hematology.Heparin-induced thrombocytopenia (HIT) is characterized by a high incidence of thrombosis, unlike other antibody-mediated causes of thrombocytopenia. We have shown that monocytes complexed with surface-bound platelet factor 4 (PF4) activated by HIT antibodies contribute to the prothrombotic state in vivo, but the mechanism by which this occurs and the relationship to the requirement for platelet activation via fragment crystallizable (Fc)γRIIA is uncertain. Using a microfluidic model and human or murine blood, we confirmed that activation of monocytes contributes to the prothrombotic state in HIT and showed that HIT antibodies bind to monocyte FcγRIIA, which activates spleen tyrosine kinase and leads to the generation of tissue factor (TF) and thrombin. The combination of direct platelet activation by HIT immune complexes through FcγRIIA and transactivation by monocyte-derived thrombin markedly increases Annexin V and factor Xa binding to platelets, consistent with the formation of procoagulant coated platelets. These data provide a model of HIT wherein a combination of direct FcγRIIA-mediated platelet activation and monocyte-derived thrombin contributes to thrombosis in HIT and identifies potential new targets for lessening this risk.

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